Remarks

Applicant has carefully considered this Application in connection with the Examiner's Action, and respectfully requests reconsideration of this Application in view of the foregoing amendment, and the following remarks.

Applicant has amended Claim 3 and added new claims 7, 8 and 9. Support for the amendments can be found in the specification as filed. Specifically, support for newly added claims 7, 8, and 9 can be found at paragraph [0006] of Applicant's disclosure. No new matter has been added.

Accordingly, Claims 1-9 are presently pending in the Application.

I. Rejection under 35 U.S.C. § 112, First Paragraph

Claim 3 stands rejected under 35 U.S.C. § 112, First Paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claim contains subject matter which was not described in a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner first contends that it is not possible to ascertain whether Applicant's claim to a method of treatment of dermatological diseases by co-administering additive/synergistic effective amounts of 33-epichloro-33-desoxyascomycin and a retinoid, such as tazarotene, exists. Applicant respectfully traverses the rejection.

The MPEP at 2163.02 states that an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Using this standard, Applicant's Claim 3 satisfies the written description requirement for the following reasons.

Applicant guides the Examiner to paragraphs [0046], [0048], [0063] and [0066] of Applicant's specification, where Applicant discusses additive/synergistic ratios of macrolide T-cell immunomodulator or immunosuppressant to retinoid for compositions according to the Applicant's invention. An exemplary means of determining synergy

between two drugs is discussed at [0046]. Specific ratios of macrolide to retinoid in accordance with the present invention are provided in paragraph [0063] as well as dosage guidelines at paragraph [0066], including modifications in dosage depending on the route of administration. When the paragraphs cited above are considered with the data presented in the Table, which summarizes the detailed experimental example discussed at paragraphs [0047] through [0051], one skilled in the art would recognize that Applicant was in possession of the invention as recited at Claim 3.

Moreover, while the Examiner expresses concern regarding whether or not the entire genus of retinoids would produce the purported synergism when combined with pimecrolimus, Applicant would like to highlight that such species of retinoids recited at Claim 3 are known to operate by the same physiological mechanism. Specifically, retinoid actions are mediated through nuclear retinoic acid receptors (RARs), which bind to retinoids and DNA and function as transcription factors. (See Hardmann, page 1599.) Various modifications to retinol have been made, mainly in attempts to lessen the side effects seen with retinol, such as skin irritation. One skilled in the art would recognize that common retinol derivatives, as recited by Applicant, share the same mode of action on epithelia and, based on the Example provided in the specification, would recognize that the disclosed retinoids would be suitable for co-administration with pimecrolimus. Thus, when considered with the discussion above regarding synergy, Claim 3 complies with the written description requirement of §112, first paragraph regarding possession of the invention.

The Examiner goes on to state that Claim 3 is rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for treatment of contact dermatitis, does not reasonably provide enablement for prevention, prophylaxis as well as curative treatment, because Applicant has defined treatment to include curative treatment. Applicant respectfully asserts that in light of the amendments to Claim 3, this point of the rejection is moot.

The Examiner has interpreted Applicant's method of treatment claim in light of a statement in the specification at paragraph [0044] wherein Applicant defines the term "treatment". Paragraph [0044] refers to treatment that includes prevention, namely prophylactic as well as curative treatment. The definition of treatment, however, does

not impose a requirement that all treatment result in prevention and cure. The definition merely reflects that some treatments could include a cure of the condition. Likewise, some treatments result in preventing the condition from returning. While in other instances, treatment manages symptoms of a condition.

Thus, while treatment, as defined by Applicant, could include treatment or prevention of a condition, each outcome is not required. The term was intended to include various degrees of healing. Applicant respectfully asserts that one skilled in the art would recognize the distinction.

Stedman's Medical Dictionary defines curative as "1. that which heals or cures, OR 2. tending to heal or cure." Likewise, Stedman's defines "heal" as "to restore to health". Prophylactic treatment is defined by Stedman's Medical Dictionary as "the institution of measures designed to protect a person from an attack of a disease to which the person has been or is liable to be exposed." Thus, Applicant sought to point out and capture the various degrees by which a person suffering from a condition can be restored to health — either the condition can be prevented from occurring, the condition can be made less severe or more tolerable, or the person can be returned to a healthful state experienced prior to onset of the condition. One skilled in the art would not interpret the claims as providing an absolute cure —completely, totally, absolutely or permanently eradicated, as asserted by the Examiner — for each condition stated.

Further supporting the assertion that Applicant did not intend such a stringent definition of the term "treatment" as interpreted by the Examiner, Applicant points out that "treatment" is used separately and distinctly from the term "prevention" throughout Applicant's specification. Specifically, at paragraphs [0053], [0059], and [0060], Applicant discusses a method of "treatment" or "prevention" of a dermatological disease. Treatment refers to "treatment of dermatological conditions in which inflammation is involved" (See Para [0043]). Thus, it is Applicant's contention that treatment — as defined in the application — was intended to include relieving symptoms of inflammation, as well as preventing the onset of inflammation, however not imposing a requirement that symptoms be relieved, as well as prevented, by administering the combination of compounds disclosed at Claim 1. One skilled in the art

would appreciate that the claims do not evoke a statement that Applicant's method can absolutely and permanently (as the Examiner has stated) cure each condition.

Nevertheless, Applicant has amended Claim 3 to reflect a method of treating a condition comprising — administering to a subject suffering from a dermatological disease such as eczema, atopic dermatitis, acne, psoriasis, skin aging, sun damage, post-peel erythema or stretch marks, an additive/synergistically effective amount of a composition of Claim 1. "Treat" is a standard medical term with a generally accepted definition "to manage a disease by medicinal, surgical or other measures; to care for a patient medically" (See Stedman's Medical Dictionary).

Applicant's specification clearly shows that the composition of Claim 1 is effective at improving the condition of contact dermatitis when compared to standard treatment of pimecrolimus alone or tazarotene alone, as shown in Table 1 of the specification. As such, Applicant respectfully asserts that the specification provides sufficient support to allow one skilled in the art to practice Applicant's invention.

As such, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of Claim 3 under 35 U.S.C. § 112, First Paragraph.

II. Rejection under 35 U.S.C. § 103(a)

Claims 1 – 4, and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ormerod et al. (WO 99/24036) in view of Hardman et al. Applicant respectfully traverses the rejection.

The Examiner cites Ormerod for teaching topical formulations and method of treatment of a dermatological condition comprising an immunosuppressive macrolide and a permeation modulator, which when applied to the skin produces a minimal systemic effect.

Ormerod, however, is solely directed to topical formulations. Ormerod discloses formulations in which significant absorption of the said drugs into the systemic system is avoided. (Ormerod, p. 5, lines 27 – 32) The formulations of Ormerod are specifically suited for passage of drug across the stratum corneum, while avoiding systemic exposure, thereby producing minimal systemic effect. (Ormerod, p. 3, lines 7 – 10 and p. 3, lines 13 – 21) Nowhere does Ormerod teach an immunosuppressive agent formulation for oral or i.v. administration as expressly taught by Applicant. Nor does

Ormerod teach an immunosuppressive agent in combination with a retinoid for treating dermatological conditions as expressly required by Applicant's Claim 1 or Claim 3.

Applicant respectfully asserts that because Ormerod fails to teach an immunosuppressive agent in combination with a retinoid, and because it is solely directed at topical formulations and explicitly seeks to avoid a systemic effect, Ormerod teaches away from Applicant's invention.

The Examiner goes on to cite Hardman for teaching the utility of retinoids and antibiotics in the treatment of dermatological diseases. Hardman does not teach, nor does Hardman even mention the macrolide T-cell immunomodulator 33-epichloro-33-desoxyascomycin, nor any immunosuppressive agents for that matter, alone or in combination with a retinoid, for treating dermatological conditions. A retinoid in combination with an antibiotic is not the equivalent of a retinoid and a macrolide T-cell immunomodulator or immunosuppressive, such as 33-epichloro-33-desoxyascomycin. Specifically, an antibacterial, as disclosed by Hardman, does not have the same mode of action on inflammation as 33-epichloro-33-desoxyascomycin taught by Applicant.

Applicant respectfully asserts that the references cited by the Examiner, singularly or in combination, fail to teach the limitations of Applicant's claims because the references fail to teach or suggest a method of treating a condition, comprising administering to a subject suffering from a dermatological disease, such as eczema, atopic dermatitis, acne, psoriasis, skin aging, sun damage, post-peel erythema or stretch marks, an additive/synergistically effective amount of a composition comprising 33-epichloro-33-desoxyascomycin in combination or association with an etretinate, isotretinoin or tazarotene, wherein administration is oral, intravenous or topical. As such, the references do not teach each and every element of Applicant's claimed invention.

At the time of the invention, not only was there simply no disclosed use of 33-epichloro-33-desoxyascomycin in combination with a retinoid for the treatment of dermatological diseases, there was no suggestion or motivation in the art to arrive at Applicant's invention. Applicant respectfully asserts that a person of ordinary skill in the art would not be motivated or suggested to combine the references as suggested by the Examiner.

For instance, while the Examiner cites *In re Kerkhoven* as the basis for the prima facie obvious rejection, the Examiner has not considered an important aspect of that case: the holding was based on the absence of unexpected results. Applicant discusses, at paragraph 0002, the surprising and unexpected nature of the results associated with the invention. As noted above in the discussion of Ormerod, previous use of immunosuppressive macrolides for dermatological conditions sought to avoid systemic dissemination. For instance, Ormerod required a permeation modulator to target partial absorption into the dermis, specifically to avoid adverse side effects related with systemic absorption of immunosuppressives. (See Ormerod, Page 5, lines 10 – 33.) Thus, Applicant respectfully asserts that it is not prima facie obvious, as the Examiner contends, to merely combine two compositions taught in the prior art useful for a similar purpose.

Moreover, it is legally insufficient to conclude that a claim is obvious just because features of a claim can be independently shown in the art. The claimed combination of Applicant's invention is not suggested by the prior art and the art, when combined, is not a predictable use of prior art elements for their established functions. Applicant believes that such a conclusion could only be drawn through impermissible hindsight.

For instance, the Examiner states that 33-epichloro-33-desoxyascomycin is disclosed to be effective in the treatment of dermatological disease. The cited teaching, however, is for topical application only. Nowhere is there a teaching or suggestion of oral dosage forms or intravenous forms of 33-epichloro-33-desoxyascomycin for the treatment of dermatological conditions, or a suggestion that the efficacy of 33-epichloro-33-desoxyascomycin would be improved by co-administration with a retinoid.

No use of an additive/synergistically effective amount of 33-epichloro-33-desoxyascomycin in combination with a retinoid for treating a dermatological condition, as required by Applicant's claims is taught or suggested by the references cited by the Examiner. As such, Applicant respectfully requests that the rejection under 35 U.S.C. §103 (a) be reconsidered and withdrawn.

III. Conclusion

In view of the foregoing, Claims 1-9 are in condition for allowance, and Applicant earnestly solicits a Notice of Allowance. If the Examiner believes, for any reason, that

personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Amendment and Reply is respectfully requested.

Respectfully submitted,
Montgomery, McCracken, Walker & Rhoads, LLP

Kristin Mazany Nevins
Attorney for Applicants
Registration No. 56,775

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123 South Broad Street
Philadelphia, PA 19109-1099
Tel: (215) 772.7655